## DETAILED ACTION

### *Status of the Claims*

Claims 1-12 are currently pending and are the subject of this Office Action. This is the first Office action on the merits of the claims.

### *Priority*

The earliest effective U.S. filing date afforded the instantly claimed invention has been determined to be 9/16/2002, the filing date of provisional application No. 60/411314 to which the instant application claims priority via its status as a national stage 371 application of PCT application CA2003/001407.

### *Specification*

The title of the invention is not adequately descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Specifically, the title should more accurately reflect how the claimed process aims to accelerate recovery from trauma.

### *Claim Objections*

Claim 11 is objected to because of the following informalities: the abbreviation "PG" should be written-out as "phosphatidylglycerol" for clarity in this claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 are rejected under 35 U.S.C. 101 as being directed to non-statutory subject matter. Patent eligible subject matter is limited to a process, machine, manufacture, or composition of matter. Claims 1-6 are considered "Use Claims," which are not covered by any of the four statutory categories, and are therefore not eligible for a patent.

### *Claim Rejections - 35 USC § 112 (1st Paragraph)*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the pre-treatment of physical trauma in circumstances when it is clear that such trauma will ensue (e.g. prior to scheduled surgery) using liposomes containing phosphatidylglycerol, does not reasonably provide enablement for either treatment of physical trauma using "a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups" or treating a mammalian patient *about to or likely to suffer* such trauma when such trauma is unexpected or not reasonably anticipated. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

2. In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;

2) the scope or breadth of the claims;

3) the state of the prior art;

4) the predictability or unpredictability of the art;

5) the relative skill of those skilled in the art;

6) the presence or absence of working examples;

7) the amount of direction or guidance presented and,

8) the quantity of experimentation necessary.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

**Nature of the invention and claim scope:** The instant claims are drawn to a process of treating a mammalian patient suffering from physical trauma or treating a mammalian patient at risk of suffering such trauma by administering to the patient liposomes comprising phosphor-glycerol groups which beneficially modify levels of inflammatory cytokines due to the trauma.

**State of the prior art:** Liposomes as drug/antigen carriers and targeted liposomal drug/antigen delivery are well known in the art, and methods for producing liposomes with phosphatidylglycerol as a major component are routine. However, formulation of

liposomes as functional dosage forms to treat a specific disease state in mammals is still a very complex practice since liposomes must meet a variety of criteria in order to be functional. These criteria include, *inter alia*, proper size, stability, lipid composition, and the presence or absence of other active agent(s) conjugated to the liposome surface. There is little in the prior art regarding the immunogenic effects of liposomes, and phosphatidylglycerol in particular.

**Degree of predictability or unpredictability in the art:** Currently, the vast majority of liposomal formulations encapsulate or otherwise carry some type of active agent(s) to exert their effect. The effectiveness of liposomes carrying no active agent other than the claimed phosphatidylglycerol groups has not been well-established.

**Relative skill possessed by those in the art:** The level of skill in the art is high and is at least that of a medical doctor or Ph.D. scientist with several years of experience in the field(s) of liposome formulation and immunology.

**Presence or absence of working examples:** Two examples were provided, only one of which was included in provisional application 60/411,314. Both examples deal with rodent models of trauma, example 1 is a rat model and example 2 is a mouse model. In the first example, the body temperature of the rodents is monitored following a surgical procedure, and in the second example body weight is monitored following a surgical procedure. Only phosphatidylglycerol-containing liposomes are administered to the rodents in these examples. As noted above, the scope of the claims is directed to phosphatidylglycerol-containing *entities* that are taken up by the patient's immune cells, thereby producing a benefit via effects mediated by these cells. Applicants do not

demonstrate how one can correlate the results of these studies to a general effect of any other type of phosphatidylglycerol-containing entities (for example, synthetic beads comprising phosphatidylglycerol) on pro- or anti- inflammatory cytokines. No data is provided to show what effect the claimed phosphatidylglycerol-containing entities have on immune cells, cytokines, or any other immunologic parameter. Furthermore, applicants merely state that "The results are predictive of the effects on other mammals, including humans." It is well known that the immune system of rodents is significantly different from that in humans, for instance see McGeachy *et al.* (McGeachy, M.J. and Cua, D.J. (2008) Immunity 28(4): 445-453; hereinafter McGeachy *et al.*) (for example, Figure 1).

**Amount of guidance or direction provided:** No guidance is provided in the specification regarding the treatment of a patient already suffering from physical trauma. The only guidance in the specification provided for pre-treatment prior to a surgery is found in the last sentence of paragraph [0026], and this is identical to the information provided in the examples. It is noted that this section of paragraph [0026] was not present in the original provisional application. Omitted details of particular relevance involve how one would identify and treat a patient *at risk for trauma*, especially one at risk for unanticipated accidental injuries. Since everyone is at risk for an unanticipated accidental injury, this possible limitation suggests that everyone on Earth would be such a patient and would fall within the scope of the instant claims.

**Quantity of experimentation required to make and use the invention:** In view of the above discussion, the state of the art with regard to producing liposomes with the

claimed effects on cytokines is highly complex and sufficiently unpredictable such that the skilled artisan would have been required to undertake undue experimentation to determine the exact manner and/or process of selecting patient(s) at risk for unanticipated trauma and determining the appropriate treatment regimen to treat patients who have already experienced trauma (but were not pre-conditioned). Absent such direction or guidance as to how the skilled artisan would go about making these determinations, one of ordinary skill in the art would have no alternative recourse but to undertake an exhaustive, and, thus, unduly burdensome search of methods to use the claimed process.

***Claim Rejections - 35 USC § 112 (2nd Paragraph)***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-6 provide for the use of "a medicament for treating a mammalian patient suffering from physical trauma, " but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

4. Claims 1-6 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper

definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

5. Claims 7-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 7, it is not clear whether the phrase in parentheses "(by surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like)" is a limitation or whether it is merely listing disclosed examples and/or embodiments. Description of examples or preferences is properly set forth in the specification rather than the claims. Since it is unclear whether the phrase in parentheses is a limitation, and thus part of the claimed invention, this phrase renders the claim indefinite. Subsequent claims 8-12 depend on claim 7 and are thus indefinite as well. See MPEP § 2173.05(d).

6. Additionally, the phrase "with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines" renders claim 7 and dependent claims thereon indefinite. The claim recites two examples of effects mediated by cells of the patient's immune system. However, it is unclear whether the claimed beneficial effects are limited to these two examples. Description of examples or preferences is properly set forth in the specification rather than the claims. Since it is unclear whether this phrase is a limitation, and thus part of the claimed invention, this phrase renders the claim indefinite. Subsequent claims 8-12 depend on claim 7 and are thus indefinite as well. See MPEP § 2173.05(d).

7. With regard to the phrases discussed in paragraphs 5 and 6, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 7 recites the broad recitation physical trauma, and the claim also recites "(by surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like)" which is the narrower statement of the range/limitation. Claim 7 also recites the broad recitation accompanying beneficial effects, and the claim also recites "including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines" which is the narrower statement of the range/limitation.

8. Additionally, the term "similar" in claim 7 is a relative term which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in

the art would not be reasonably apprised of the scope of the invention. It is acknowledged that a brief discussion of entity size is presented in paragraph [0024] of the instant specification. However, no formal definition of the term "similar" is presented. Furthermore there is no discussion of the size of an "apoptotic mammalian cell or apoptotic body" and the discussion of paragraph [0024] cannot be read into the claims.

9. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 9 recites the limitation "phosphatidylglycerol liposomes" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 9 depends from claim 7, however claim 7 does not recite "phosphatidylglycerol liposomes," thus the claim is indefinite.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 7-9 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Stokes *et al.* (U.S. Patent No. 5,932,563); Issued Aug. 3, 1999) (hereinafter Stokes *et al.*).

Instant claim 7 recites:

> A process of treating a mammalian patient suffering from physical trauma, or treating a mammalian patient at risk of suffering such trauma (by surgical treatment, or by suffering unanticipated accidental injuries, battle injuries or the like) to lessen the severity of and/or accelerate the recovery from such trauma, which comprises administering to the patient an effective immune system modifying amount of immune system-modifying entities, each comprising a body of a size similar to an apoptotic mammalian cell or apoptotic body, and having exposed on its surface phospho-glycerol groups, the entities being capable of being taken up by cells of the patient's immune system with accompanying beneficial effects including inhibition of pro-inflammatory cytokines and/or promotion of anti-inflammatory cytokines.

11. Stokes *et al.* disclose a method for treating spinal cord trauma by administering liposomes to a patient (abstract) and inducing an immune response (column , lines 46-54; column 5, lines 7-13). Stokes *et al.* teach that suitable lipids for the disclosed liposomes include phosphatidyl glycerol (column 2, lines 12-14). By virtue of the presence of phosphatidylglycerol in the membrane, the liposomes have phospho-glycerol groups exposed on their surface. Stokes *et al.* further teach that the liposomes of their invention are capable of being taken up by macrophages (i.e. cells of the patient's immune system) (column 2, lines 10-11). Since both Stokes *et al.* and the claims of the instant application involve methods to treat trauma by stimulating a patient's immune system with phosphatidylglycerol-containing liposomes, it is reasonable to expect the same beneficial effects as those of instant claim 7. Thus, the patent to Stokes *et al.* reads on each element of instant claims 7 and 8. Additionally, Stokes *et al.* teach that the liposomes of their invention have a size of "less than 6 microns in diameter, more preferably about 1 micron in diameter," (column 2, lines 18-20) reading on instant claims 9 and 12.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 7-9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gristina *et al.* (U.S. Patent No. 5,770,234; Issued Jun. 23, 1998; A2 of record on IDS of 4/19/05) (hereinafter Gristina *et al.*) in view of See *et al.* (U.S. Patent No. 6,015,576; Issued Jan. 18, 2000) (hereinafter See *et al.*).

8. Gristina *et al.* disclose a method for stimulating a patient's immune system using phagocytosable particles to prime macrophages (abstract). Gristina *et al.* teach that this technique may be used for, *inter alia*, the pre-treatment of patients undergoing surgery, the treatment of accident victims suffering from wounds or burns, or the prophylactic

treatment of personnel being sent to war zones and natural disaster sites (column 2, lines 42-51). Gristina *et al.* disclose that this technique is applicable to traumatized tissues (column 3, lines 35-46) and further teach that the particles of their invention may be liposomes (column 5, lines 5-10). While Gristina *et al.* teach the use of several common phospholipids (column 5, lines 7-10) the use of phosphatidylglycerol in the liposomes is not disclosed. However, See *et al.* disclose a method for inducing an immune response in a mammal comprising administering liposomes to a subject (abstract). See *et al.* teach that the disclosed liposomes may be made of "any suitable phospholipid," which may include phosphatidyl glycerin (column 4, lines 19-23), which is synonymous with phosphatidyl glycerol. By virtue of the presence of phosphatidylglycerol in the membrane, the liposomes have phospho-glycerol groups exposed on their surface. Since phosphatidylglycerol is a standard component of liposome membranes, and since phosphatidylglycerol is taught by See *et al.* for use in immune-stimulating liposomes, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute phosphatidylglycerol as a component (i.e. substitute one known liposome phospholipid for another) to construct phosphatidylglycerol-containing liposomes for use in the method of Gristina *et al.* See *et al.* also teach that the liposomes of their invention are taken up by macrophages (i.e. cells of the patient's immune system), initiating a systemic immune response (column 3, lines 45-54). See *et al.* teach that one aspect of the immune response initiated by the liposomes is the production of cytokines by the macrophages (column 3, lines 21-24). Furthermore, since both Gristina *et al.* and the claims of the instant application involve

methods to treat trauma by stimulating a patient's immune system with liposomes, and since See *et al.* involves a method to stimulate a subject's immune system with phosphatidylglycerol-containing liposomes, it is reasonable to expect the same beneficial effects as those of instant at claim 7 when phosphatidylglycerol is used in the method of Gristina *et al.*, including the production of at least some anti-inflammatory cytokines. Thus, Gristina *et al.* and See *et al.* render obvious each element of instant claims 7 and 8.

9. Gristina *et al.* and See *et al.* teach the process of claim 7 as discussed above (paragraph 8). Additionally, Gristina *et al.* teach that the particles of their method "must be of phagocytosable size (0.1-10 μM)" (column 2, lines 57-58) including "liposome particles of size range 10 nanometers to 10 micrometers in diameter," (column 5, lines 5-7) and See *et al.* teach that the liposomes of their invention have a size "of from 20 nm-20 microns" (abstract), reading on instant claims 9 and 12.

10. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gristina *et al.* and See *et al.* as applied to claims 7 and 8 above, and further in view of Schneider et al. (U.S. Patent No. 6,110,443; Issued Aug. 29, 2000) (hereinafter Schneider et al.).

11. Gristina *et al.* and See *et al.* teach the process of claims 7 and 8 as discussed above (paragraph 8). Gristina *et al.* and See *et al.* do not teach the claimed weight % range for phosphatidylglycerol. However, Schneider *et al.* disclose methods for producing empty liposomes (column 4, lines 30-39) comprising from 50-100% of a surfactant, which can be phosphatidylglycerol (column 6, lines 26-33). While other additives and surfactants can be added to these liposomes, it is clear from the

disclosure of Schneider *et al.* that the film-forming surfactants of their invention are intended to be the major component of the formulation (column6, lines 43-46, and 62-65), and would thus fall within the range of 50-100% by weight of the liposome. Since phosphatidylglycerol is a standard component of liposome membranes, it is taught by See *et al.* for use in immune-stimulating liposomes, and it is taught in the required weight % range by Schneider *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to substitute phosphatidylglycerol as a component in the required weight % range to construct phosphatidylglycerol-containing liposomes with optimal immuno-active properties for use in the method of Gristina *et al.*

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Patent Application No. 10/565,360

12. Claims 7-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 7-10 of copending Application No. 10/565,360. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '360 claims

anticipates or renders obvious that of the instant claims. Claim 1 of the '360 application recites a method of preventing or treating an acute inflammatory disorder comprising administering bodies carrying phosphate-glycerol groups wherein the bodies have a size from about 20 nm to 500 μm. Since trauma results in acute inflammation, the '360 application can be considered a species of trauma and anticipates instant claims 7-12. It is noted that the recitation in instant claim 7 of the bodies being capable of being taken up by immune cells and the accompanying effects are inherent properties to the bodies of size and composition as claimed in '360 claim 1. Claims 2 and 7-10 of the '360 application also read on the instant claims.

U.S. Patent Application No. 10/348,601

13. Claims 7-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-31 of copending Application No. 10/348,601. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '601 claims anticipates or renders obvious that of the instant claims. Claim 1 of the '601 application recites a method for treating a disorder involving inappropriate cytokine expression comprising administering bodies carrying phosphate-glycerol groups. Since inappropriate cytokine expression is a result of trauma, the '601 application anticipates instant claims 7-12. It is noted that the recitation in instant claim 7 of the bodies being capable of being taken up by immune cells and the accompanying effects are inherent properties to the bodies of size and composition as claimed in '601 claim 30. Claims 58-59 of the '601 application also read on the instant claims.

U.S. Patent Application No. 11/946,802

14. Claims 7-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-59 of copending Application No. 10/946,802. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the '802 claims anticipates or renders obvious that of the instant claims. Claim 18 of the '802 application recites a method for treating an inflammatory disorder comprising administering bodies carrying phosphate-glycerol groups. Since inflammation is a direct result of trauma, the '802 application anticipates instant claims 1-12. It is noted that the recitation in instant claim 7 of the bodies being capable of being taken up by immune cells and the accompanying effects are inherent properties to the bodies of size and composition as claimed in '802 claims 20, 48, and 50. Claims 51-59 of the '802 application also read on the instant claims.

## ***Conclusion***

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin S. Orwig whose telephone number is (571)270-5869. The examiner can normally be reached Monday-Friday 7:00 am-4:00 pm (with alternate Fridays off). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached Monday-Friday 8:00 am-5:00

pm at (571)272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KSO

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